REMARKS

Claims

Claims 33-35, 38, 42-48, 50-59, 119-132, 137-142, and 144-173 are pending. Claims 119-132 and 144-173 are currently under examination, with the remaining claims withdrawn as directed to non-elected subject matter.

Applicants' Invention

The pending claims are directed to GDF-8 propeptides that have an increased in vivo or in vitro half life. The invention relates to the discovery that the natural GDF-8 propeptide has a relatively short in vivo half-life (see specification at page 4, lines 14-16). The claimed invention is further based on the unexpected discovery that mutation at a particular site within the GDF-8 propeptide sequence, the aspartate residue corresponding to Asp 76 of SEQ ID NO:5, renders the modified GDF-8 propeptide surprisingly effective as an inhibitor of GDF-8 activity (see Reply filed February 20, 2004, and the accompanying Declaration of Neil M. Wolfman).

The modified GDF-8 propeptides of the present claims are set forth in independent claims 119, 144, 165, 171, and 173. Particular propeptide embodiments are provided in dependent claims 120-131, 145-164, 166-170, and 172. Claim 132 is directed to pharmaceutical compositions comprising the modified GDF-8 propeptides. The withdrawn claims are directed to methods to make or use the claimed GDF-8 propeptides, and remain pending in order to be considered for rejoinder under MPEP § 821.04.

Information Disclosure Statements

In this Office Action, the Examiner acknowledges consideration of references provided on March 13, 2003, November 12, 2004, and June 24, 2005, with the exception of the International Search Report of PCT/US02/30452 and the International Search Report of PCT/US02/03467. The Examiner states that these international search reports (ISRs) were not considered because they allegedly are not in conformance with MPEP § 609. The Examiner also offers to consider the individual references that are cited in the ISRs, if the Applicants provide them. Applicants note that the references cited in the ISRs were submitted previously, and they have been considered and initialed by the Examiner.

Applicants believe that the submission of the two international search reports complies with MPEP § 609, and note that 37 CFR § 1.98 requires consideration of the reports. MPEP § 609 instructs that information submitted in an information disclosure statement that complies with the content requirements of 37 C.F.R. § 1.98 and is filed in accordance with the procedural requirements of 37 C.F.R. § 1.97 shall be considered by the Office. (MPEP § 609, "Once the minimum requirements of 37 CFR 1.97 and 37 CFR 1.98 are met, the examiner has an obligation to consider the information.").

The International Search Reports of PCT/US02/30452 and PCT/US02/03467 are provided as "other information submitted for consideration by the Office" under 37 C.F.R. § 1.98(a)(1). The ISRs are relevant for their citation and classification of specific references, for example. A copy of each ISR was provided on March 13, 2003, complying with 37 C.F.R. § 1.98(a)(2). Thus, Applicants respectfully ask the Examiner to consider and acknowledge consideration of the cited international search reports.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejects all pending claims that are under examination as allegedly non-enabled and not adequately described due to claim terms "modified" and "at least 75% identical (to SEQ ID NO:5 or its fragments)."

Specifically, the Examiner alleges that the terms "modified" and "modifies" do not limit the possible modifications to the GDF-8 propeptide or a fragment thereof, nor do the terms limit the potential modifications to the aspartate residue at position 76. The Examiner also alleges that the claims include "no functional limitations [for the modified propeptides], apart from the inherent activities of the GDF-8 propeptide." The Examiner further states that claims 119-132 and 144-173 are directed to amino acid sequences that are at least 75% identical to SEQ ID NO:5. On this basis, the Examiner rejects all pending claims under 35 U.S.C. § 112.

The Applicants respectfully submit that the Examiner has misinterpreted the claims. The term "modified GDF-8 propeptide" is specifically defined in the claims as a GDF-8 propeptide having a specific modification in the aspartate residue corresponding to Asp 76 of SEQ ID NO:5 and an increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8 propeptide. This construction is consistent with the use of the term "modified GDF-8 propeptide" in the specification at page 9, lines 18-29, and at page 19, lines 23-29. Thus, the term "modified" does not refer to undefined structural features, but rather refers specifically to the structural and functional modification to GDF-8 propeptides defined in the claims.

Further, the increased half-life of the modified propeptide is not an inherent property of the unmodified GDF-8 propeptide, and it is incorrect to posit that claims 119-

132 and 144-173 merely encompass an amino acid sequence that is at least 75% identical to SEQ ID NO:5. All modified GDF-8 propeptides encompassed by the claims include a specific mutation at Asp 76 and specific functional characteristics not present in native GDF-8 propeptides. Moreover, dependent claims 147-159 further limit the "at least 75% identical" structural limitation, and provide various requirements (ranging from 80% to 95% or more identity). Applicants also note that independent claim 171 includes no percent identity limitation. The claims delineate and refine the stabilizing modification at the aspartate residue at position 76, for example in claims 119, 120, 144-146, 159, 165, 166, and 171-173. Thus the Examiner's basis and argument for rejecting the claims under 35 U.S.C § 112 is in error, and the rejections should be withdrawn.

Applicants note that GDF-8 is a known protein that is a member of the well characterized TGF-β superfamily of growth regulatory factors (see, e.g., the specification at page 1, lines 21-26). The Examiner's rejections based on sweeping characterizations of "any given protein" or "a protein found in the database" are therefore inappropriate (see Office Action at page 3, lines 16-19 and page 4, lines 12-13). The sequence, domain structure, and functional properties of GDF-8 proteins were well known at the time of filing, and are set forth in the specification (see, e.g., pages 1-3 and Examples 1-6). The specification also discloses the well known structure and functional characteristics of GDF-8 and its propeptide, as well as its structure-function relationship to other TGF-β family members (see, e.g., page 2, lines 20-29).

The specification discloses the sequences of mouse and human GDF-8 propeptides in Figures 7 and 11, and discloses GDF-8 proteins from bovine, dog, cat,

chicken, mouse, rat, porcine, ovine, turkey, baboon, and fish, as well as a reference that aligns GDF-8 proteins from 10 species (see page 7, lines 8-13). One skilled in the art, based on this disclosure and the known characteristics of GDF-8 propeptides, could therefore make and use the modified propeptides as claimed without undue experimentation. Similarly, based on the knowledge of the skilled artisan, the specification conveys that the inventors had possession of the claimed invention to the skilled artisan.

Thus, Applicants respectfully request reconsideration and withdrawal of the enablement and written description rejections of claims 119-132 and 144-173.

Rejections under 35 U.S.C. § 112, second paragraph

Applicants thank the Examiner for withdrawing the indefiniteness rejection of claims 119-132 and 144-171, and appreciate the Examiner's acknowledgement that the claims comply with 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 102(a) of Claims 144-159

In the previous Office Action dated January 24, 2005, the prior Examiner had rejected claims 144-159 as allegedly anticipated by WO 200043781, alleging that the claims did not require that the modified GDF-8 propeptide have a mutation at position 76. In response, Applicants amended claim 144 to correct a typographical error. This correction clarified the antecedent basis of "amino acid sequence" in part (ii) of claim 144 and obviated the rejection. In this Office Action, the anticipation rejection of claims 144-152 is withdrawn, but the rejection of claims 153-159 is maintained.

Applicants note that claims 153-159 depend from claim 144 and encompass all of its limitations. Applicants respectfully submit, therefore, that the rejection is necessarily in error. Claim 144 encompasses modified GDF-8 propeptides comprising a GDF-8 moiety and an optional heterologous moiety, wherein the GDF-8 moiety has a mutation in the amino acid sequence at position 76 of SEQ ID NO:5. The term GDF-8 moiety is further narrowed in claims 153-159.

In order to anticipate, a reference must disclose each and every limitation of a claim, either expressly or inherently. WO 200043781 does not disclose each of the limitations of claim 144. Consequently it cannot disclose each of the limitations of dependent claims 153-159. Therefore, the Applicants respectfully ask the Examiner to withdraw the rejection of claims 153-159 under 35 U.S.C. § 102.

New Rejection under 35 U.S.C. § 102(a) of Claims 119-132

For the first time in this Office Action, the Examiner rejects claims 119-132 as allegedly anticipated by WO 200043781. The Examiner now alleges that as written, there is no requirement in the claims that the modified GDF-8 propeptide have a mutation at position 76. The Examiner further states "that limitation refers only to the moiety of section (b) of claim 119."

With due respect, Applicants submit that this rejection can only be based on erroneous construction of the claims. Claim 119 recites "a modified GDF-8 propeptide comprising. . . [parts (a) or (b)] "wherein the modified GDF-8 propeptide has a mutation that modifies the aspartate residue corresponding to Asp 76 of SEQ ID NO:5. . . " (emphasis added). Thus, the modified GDF-8 propeptide contains a mutation that

modifies the aspartate residue. There is no "moiety of section (b)" in claim 119. Accordingly, Applicants ask the Examiner to reconsider and withdraw the rejection that claims 119-132 are anticipated by WO 200043781.

Rejection under 35 U.S.C. § 103(a) of Claims 160-164

The Examiner maintains an obviousness rejection of claims 160-164 from the previous Office Action, stating only that for the reasons set forth in the Office Actions of January 24, 2005 and August 21, 2003, the claims are unpatentable over WO 200043781.

First, Applicants note that the obviousness rejection of August 21, 2003 was overcome when Applicants amended the claims to make it clear that the modified GDF-8 propeptides comprise a mutation at the residue corresponding to position 76 of SEQ ID NO:5, for example (See Office Action dated May 14, 2004). Further, the obviousness rejection posed on January 24, 2005, like the anticipation rejection posed in the same document relating to claims 144-159 (see above), was based on the prior Examiner's identification of a typographical error in claim 144. With correction of that error in Applicants' Amendment dated June 24, 2005, claims 160-164 clearly encompass modified GDF-8 propeptides having a mutation in the amino acid sequence at the residue corresponding to position 76 of SEQ ID NO:5.

Thus, Applicants believe that this rejection is also due to misinterpretation of the claims, and respectfully ask the Examiner to reconsider and withdraw the obviousness rejection of claims 160-164.

New Rejection under 35 U.S.C. § 103(a) -- WO 200043781 and Lee

The Examiner now rejects claims 119-132 and 144-173 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 20043781 in view of Lee *et al.*, "Analysis of Site-directed Mutations in Human Pro-α2(I) Collagen Which Block Cleavage by the C-proteinase," *J. Biol. Chem.* 265:21992-21996 (1990).

The Patent Office bears the burden to establish a prima facie case of obviousness under 35 U.S.C. § 103. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re* Deuel, 51 F.3d 1552, 1557 (Fed. Cir. 1995). To support a rejection under § 103, the examiner must provide evidence to demonstrate that (1) one or more references teach or suggest all of the limitations of the claim; (2) the references provide some suggestion or motivation for one of ordinary skill in the art to modify or combine the references; and (3) one of ordinary skill in the art would have had a reasonable expectation of success on modifying the prior art references. MPEP § 2143; *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

The Examiner bears the initial burden of demonstrating that the cited references "expressly or impliedly suggest the claimed invention" with all its limitations, or she "must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985); MPEP § 2142. Applicants respectfully submit that this initial burden has not been met.

In this new obviousness rejection, the Examiner recognizes that WO 200043781 does not teach a specific mutation at the aspartate residue corresponding to position 76

of SEQ ID NO:5. The Examiner, however, alleges that this limitation would have been obvious to one skilled in the art from WO 200043781 in combination with Lee et al.

As discussed above, WO 200043781 discloses a broad genus of GDF-8 protein inhibitors, and it discloses propeptide inhibitors, but it does not disclose a mutation in the GDF-8 propeptide at the residue corresponding to Asp 76 of SEQ ID NO:5. WO 200043781 detects a 25 kDa fragment of the GDF-8 propeptide in conditioned media from transfected cells. The fragment is a carboxyl-terminal portion of the propeptide that has a DDSSD amino terminal sequence (corresponding to residues 76-80 of SEQ ID NO:5). WO 200043781 then states that cleavage at Arg 99 may result in the 25 kDa species. After showing that the 25 kDa fragment does not inhibit mature GDF-8 in a reporter activation bioassay, while the full-length propeptide does inhibit in the assay, WO 200043781 states at page 63, lines 4-7:

> This indicates that the inhibitory (or GDF-8-binding) domain is located in the N-terminus of the pro-domain, upstream of Arg 99. Thus, GDF-8 inhibitors of small molecular size may be designed based on the sequence of the pro-domain upstream of Arg 99 (see Figure 13).

This reference generally discloses "GDF-8 protein [] variants which do not possess detectable GDF-8 activity" at page 20, lines 15-17, and GDF-8 propeptides at page 22, lines 10-24. At page 21, WO 200043781 discloses mutations in a protease cleavage site at Arg 266, the site that is cleaved in the precursor GDF-8 to release the GDF-8 propeptide and mature GDF-8 proteins.

Lee describes the cleavage of pro-α2(I), a procollagen protein, by a C-proteinase to release the mature, functional collagen. Lee further teaches that a mutation of the aspartate residue within the procollagen cleavage site (FYRA-DQ) inhibits the proper

release of mature collagen. Specifically, Lee states "[s]ubstitution for a conserved Asp, which forms part of the Ala-Asp bond cleaved by C-proteinase, also blocks cleavage by endogenous C-proteinase" (Lee, page 21992).

The Examiner acknowledges that WO 200043781 does not teach any specific mutation at the aspartate residue corresponding to position 76 in SEQ ID NO:5, and that it does not teach any mutation that inactivates proteolytic cleavage at or around that site. There is no motivation in WO 200043781 to provide a GDF-8 propeptide that has a mutation at the residue corresponding to Asp 76, nor is this deficiency overcome by considering Lee.

WO 200043781 states that the inhibitory portion of the propeptide is in its amino terminal portion; it therefore cannot be reasonably read to suggest mutating the aspartate 76 residue which falls outside of this amino terminal portion to create a modified GDF-8 propeptide. Contrary to the Examiner's argument, WO 200043781 does not teach or suggest "a highly conserved proteolytic region (DDSSD)," instead it identifies DDSSD as the first five amino acids of the 25 kDa fragment. Figure 11 also shows high levels of conservation throughout the length of the propeptide portion and across ten species of GDF-8. Additionally, while the Examiner asserts that variants of GDF-8 propeptides including altered proteolytic sites are taught at pages 20-21, Applicants wish to clarify that page 20 discloses "GDF-8 or GDF-11 protein variants which do not possess detectable GDF-8 activity," and page 21 discloses mutations in the site for "cleavage of the carboxy-terminal mature peptide from the amino-terminal precursor remainder." It continues: "mutations in the conserved cleavage sequences, required for activation, can result in the synthesis of non-functional GDF-8 and GDF-11

molecules." This protease site performs a distinct biological function from the Asp 76 site, mutations inhibit GDF-8 activity by an entirely different process, and these mutations therefore provide no motivation to alter the internal GDF-8 propeptide sequence at the residue corresponding to Asp 76 of SEQ ID NO:5.

Lee similarly does not provide a motivation to alter the sequence at the Asp 76 residue, nor is there any motivation in either WO 200043781 or Lee to combine the two references. The procollagen protein described in Lee is unrelated to GDF-8 and has no significant homology to GDF-8. Similarly the sequence of the procollagen cleavage site is unrelated to the portion of GDF-8 that is cleaved. In addition, the bond cleaved by a protease in each instance differs; there is no Ala-Asp bond at the GDF-8 cleavage site.

Also contrary to the Examiner's assertion, Lee does not generally disclose "the importance of aspartate residues in rendering proteolytic sites susceptible to cleavage by C-proteinases." It examines only one aspartate in pro-α2(I). Nor is there a suggestion that a C-proteinase cleaves the GDF-8 propeptide in either reference, in the art generally, or in Li et al., "The C-proteinase that processes procollagens to fibrillar collagens is identical to the protein previously identified as bone morphogenic protein-1," *Proc. Natl. Acad. Sci. U.S.A.* 93:5127-5130 (1996), which appears to be cited by the Examiner for this proposition. Li et al. merely adds the fact that Lee's C-proteinase is identical to bone morphogenic protein-1, which is a zinc-requiring endopeptidase. Further, at page 5130 Li states that the C-proteinase (BMP-1) cleaves Ala-Asp and Gly-Asp bonds in procollagens, whereas one or ordinary skill in the art at the time the instant application was filed would appreciate that the bond cleaved in the GDF-8 propeptide is an Arg-Asp bond.

Indeed, the discovery that a metalloprotease like the C-proteinase of Lee cleaves the GDF-8 propeptide to generate the 25 kDa fragment was not made until well after the filing of the instant application (see Wolfman et al., "Activation of Latent Myostatin by the BMP-1/Tolloid Family of Metalloproteinases," *Proc. Natl. Acad. Sci. U.S.A.* 100:15842-15846 (2003), cited in the IDS filed on June 24, 2005 and considered by the Examiner on August 24, 2005). At the time of the invention, a skilled artisan could not have known that BMP-1/TLD metalloprotease was the responsible for cleaving the GDF-8 propeptide to render it inactive. Such hindsight-driven analysis of obviousness of an invention is inappropriate.

Thus, WO 200043781 does teach or suggest that Asp 76 is critical for an internal proteolytic cleavage of GDF-8 propeptide, or the biological effect of a mutation at this site. WO 200043781 does not indicate that a mutation that modifies Asp 76 of SEQ ID NO:5 in any way, or in particular the substitution, deletion, and insertion mutations described in the instant application that result in modified GDF-8 propeptides with alanine at position 76, would create a GDF-8 inhibitor with a dramatically increased half life. Lee does not overcome this deficiency because the proteolytic cleavage site defined by Lee, FYRA-DQ (see Lee, Figure 1), is unrelated to the GDF-8 propeptide sequence that immediately surrounds the proteolytic cleavage site upstream of Asp 76 (DVQR-DDSSD). The procollagen protein is structurally and functionally unrelated to GDF-8, and there is not indication in either reference or in the prior art that a related proteinase is responsible for cleavage at both sites.

Although Applicants believe that the Examiner has not established a prima facie case of obviousness, Applicants note that the declaration of Dr. Neil Wolfman, provided

earlier in prosecution of this application, demonstrates the unexpected results associated with mutation at the residue corresponding to Asp 76 (see Reply filed February 20, 2004, and the Declaration of Neil M. Wolfman filed therewith). A mutation at the Asp 76 results in increased stability of the protein in vitro and increases its biological activity in vivo as compared to wildtype propeptide. Thus, as argued previously, these unexpected properties of the claimed mutations are sufficient to rebut any prima facie case of obviousness. See *In re* Chu, 66 F.3d 292 (Fed. Cir. 1995); *In re* Soni, 54 F.3d 746 (Fed. Cir. 1995).

In light of the arguments outlined above, Applicants request that the obviousness rejection of claims 119-132 and 144-173 under 35 U.S.C. § 103(a) be withdrawn.

Additional Rejections under 35 U.S.C. § 103(a) -- in view of Chang, Simvan, or Davis

The Examiner also rejects claims 121-131, 160, and 167-170 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 200043781 in view of U.S. Patent No. 5,723,125 (Chang), U.S. Patent No. 5,116,944 (Simvan), or U.S. Patent No. 4,179,337 (Davis). Without acquiescing in these grounds for rejection, Applicants argue that the indicated claims are novel and nonobvious because the independent claims from which they depend are novel and nonobvious, as described above. Thus, Applicants respectfully request withdrawal of these rejections.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: March 6, 2006

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